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# Present status, standardization and safety issues with herbal drugs

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#### ABSTRACT

Antibiotics are the 'wonder medicines' used for battling microbes. Numerous types of antibiotics have been not only used for therapeutic purposes for decades, but have been used prophylactically across other fields such as livestock and animal husbandry. The emergence of multidrug resistance among pathogenic bacteria jeopardizes the importance of antibiotics which have transformed medical sciences before. A growing list of infections, i.e. pneumonia, tuberculosis, and gonorrhea, is becoming more difficult and sometimes impossible to treat as antibiotics become less effective. Antibiotic-resistant infections are correlated with antibiotic intake levels. It is mainly the non-judicial use of antibiotics that makes the bacteria immune. Extensive efforts are required to reduce the rate of resistance by researching emerging microorganisms, mechanisms of resistance and antimicrobial agents. Multidisciplinary strategies are required across health care environments, as well as across sectors of the environment and agriculture. Conservative new approaches including probiotics, antibodies, and vaccines have demonstrated positive results in future trials that suggest the role of these alternative options as preventative or adjunct therapies.

Keywords: Antibiotics; Antibiotic resistance; Multi drug resistance.

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#### INTRODUCTION

Bacteria and other microorganisms have the ability to resist the effects of an antibiotic they were once responsive to. Antibiotic resistance is a major concern about antibiotic overuse. Sometimes referred to as drug resistance. Antibiotics are the 'wonder drugs' used in fighting microbes. Multiple varieties of antibiotics were not only used for therapeutic reasons for decades, but have been therapeutically practiced across other industries, such as agriculture and animal husbandry. Uncertainty arose when microbes became immune to traditional antibiotics while the host remained unaware that resistance to antibiotics has arisen.<sup>[2]</sup> A growing list of pathogens, i.e. pneumonia, tuberculosis, and gonorrhea, is becoming more difficult and quite often impossible to treat as antibiotics are less effective. Antibiotic-resistant infections are correlated with antibiotic intake levels. It is primarily the non-judicial use of antibiotics which makes the microbes resistant. The repertoire of antibiotic treatment for existing or emerging hard-to-treat multidrug-resistant bacterial infections is limited, resulting in identified high morbidity and mortality. Extensive efforts are needed to mitigate the speed of resistance by examining emerging microorganisms, mechanisms of resistance and antimicrobial agents. Literature evidence suggests that knowledge about antibiotic resistance is still scarce in the population. The need to educate patients and the public is thus essential to tackle the battle of antimicrobial resistance.[3]

#### Antibiotic discovery and supremacy

To kill diseases or bacteria, antibiotics are certainly a gift to human civilization, which has saved millions. In the course of time several types of antibiotics were used for therapeutic purposes. In the mid-20th century antibiotics were seen as the "wonder drug". There was an optimistic belief at the time that communicable disease was about to come to a complete halt. The beginning of the modern "antibiotic era" has been associated synonymously with two names: Alexander Fleming and Paul Ehrlich. Antibiotics were considered a magic bullet that selectively targeted microbes that were responsible for causing the disease but would not affect the host at the same time. Fleming was the first person to warn about the possible resistance to penicillin if used too often or for a too short treatment time. Thus, the period from the 1950s to the 1970s was regarded as the golden era for discovering new classes of antibiotics. However, scientists soon discovered and developed novel β-lactam antibiotics to maintain utilizing antibiotic treatment strategies. However, in 1962 and 1968, respectively, the first case of methicillin-resistant Staphylococcus aureus (MRSA) was reported in the UK and the US, the same decade when new antibiotics were being applied.<sup>[4]</sup>

Regrettably, resistance to almost all of the antibiotics established during that period was noted with the passage of time. Later in 1972 the clinicians were presented with an antibiotic called "vancomycin" to treat MRSA. It was claimed during that period that development of resistance to vancomycin was unlikely to happen in clinical settings. Yet few cases of coagulasenegative vancomycin-resistant staphylococci were reported during the late 1970s and early 1980s. Until the early 1980s, the pharmaceutical industry developed and introduced many new antibiotics to solve the resistance problem, and the pace of antibiotic development staggered with the passage of time, so very few new antibiotics were introduced.<sup>[5]</sup> Consequently in 2015, after ~70 years since the first patient received antibiotic treatment, bacterial infection once again became a serious life threat.

Although antibiotic resistance is blossoming as a global threat at present, there are certain breakthroughs antibiotics have enacted on to humans, notably in medicine and surgery. Antibiotics have treated or prevented bacterial infections that may occur during chemotherapy or major surgeries such as replacement of the joints, organ transplantation or cardiac operations. Such magic bullets also altered the outcome of bacterial infections that increased the average life expectancy. Life expectancy in the US was 56.4 years during 1920; on the other hand, the average life expectancy at the moment in the US is about 80 years. Antibiotics have had a practical linear impact across the globe, for instance in developing nations with deprived public health infrastructure, as antibiotics reduce the morbidity and mortality rate caused by human and cattle bacterial infections.<sup>[6]</sup>

#### Epidemology

Overuse of antibiotics is mainly the main cause of the development of resistance, as Sir Alexander Fleming has also cautioned that "the public will demand (the medication) and then begin a period of violence." Antibiotics destroy sensitive bacteria but allow resistant pathogens to survive, which then replicate and flourish through natural selection. While antibiotic overuse is strongly discouraged, over prescription persists around the globe.<sup>[7]</sup> Several studies have revealed that indications of treatment, choice of agent and duration of antibiotic therapy are inappropriate in 30 percent -50% of cases. Antibiotics are used globally as a promoter of livestock growth. An estimate shows that around 80 percent of antibiotics are sold in the US for use only as growth supplements and to control animal infection. In another study, a global map of 228 countries was drawn depicting the intake of antibiotics in livestock; the total antibiotic consumption was estimated at 63.151 tons in 2010. Van Boeckel et al also expected an increase in antibiotic intake of 67 percent by 2030 which would almost double the rapidly evolving block in Brazil, Russia, India, Chinese and South Africa.<sup>[6]</sup> Chain of world fastdeveloping and highly populated nations.

# **Causes of antibiotic resistance**

Currently the multifaceted antibiotic resistance etiology has many factors at play. These include insufficient legislation and inaccuracies in use, lack of awareness of best practices that guide excessive or incompetent use of antibiotics, the use of antibiotics as a promoter of poultry and livestock growth rather than infection control, and online marketing that has rendered it unregulated low-grade antibiotic availability is very accessible.<sup>[8]</sup>

#### Divers of antibiotic resistance transmission

At the moment the knowledge of different antibiotic resistance drivers is the key to tackling this global issue. The occurrence of resistance in microbes is a process that occurs until now, selection of antibiotic resistance is driven with the use of various antibiotics in health care systems, environment, and in agriculture / livestock. Sanitation conditions, infection control requirements, water hygiene systems, medication safety, diagnostics and treatment, and travel or migration quarantine are additionally key factors that are active drivers of antibiotic resistance.<sup>[9]</sup> In addition to a mutation in different genes that reside on the microorganism's chromosome, the exchange of genetic material among organisms serves a vital role in the dissemination of antibiotic resistance. Plasmid transmission is by far the most important mechanism that can transfer antibiotic resistance genes to the host cell. Antibiotics can influence the above process by causing resistance elements to be transmitted; these pathogens can also exert selective pressure for resistance to emerge. Manifestation of resistance transfer dynamics has raised knowledge and awareness of how resistant pathogens spread from humans to humans.<sup>[10]</sup> Feco-oral route is by far the most crucial transmission route at the community level, especially for the Enterobacteriaceae entire family resistant pathogens, usually due to sanitation failure. Community-acquired (CA)-MRSA also is a

good example of the dynamics of resistance dissemination at the human-human level; Usually transmitted because of prolonged hospital stay or hospital unhygienic settings.



Figure 1: Antibiotic resistance transmission

Another important element known as "one health" also plays an important role in the dynamics of transmission of antibiotic resistance. The unreasonable use of antimicrobial development promoters in livestock is correlated with the transmission of resistance to humans through animal products; Salmonella spp are important pathogens considered throughout this aspect. are Salmonella spp. and Campylobacter spp. In addition, indistinguishable resistant mechanisms were found in human-or animalisolated bacteria. Resistant bacteria and mobile genetic elements (MGEs) can make their way from animals to humans through various means. Another concern is the environmental influence toward antibiotic resistance.<sup>[11]</sup> Metals are used as microbicides in the agricultural sector, and can contribute critically to the production of resistance. Also well known is the role of sewage systems, contamination by the pharmaceutical industry and waste management procedures in human environment transmission. A multitude of resistant pathogens were isolated from sewerage systems for pre-as well as post-treatment as represented in Figure 1.

#### Mechanism of antibiotic resistance and virulence

Bacteria live on human tissue, mucous membranes, and also inside the body. Bacteria comprise innocuous species, many of which are useful commensals and few of them are even important. Though, some of these are known infectious pathogens; these are capable of colonizing, invading, and harming the host tissue. Pathogenicity is a bacterium's ability to cause disease, and a pathogen carries a number of factors that make it easier for the bacterium to increase its degree of pathogenicity known as virulence as represented in Figure 2. Toxicity and invasiveness are among the most important properties which help a pathogen cause a disease. Virulence and the host immune status can influence the ultimate sense of balance of a course of a bacterial disease. With time, both the host and bacteria have coevolved, which may be as long as millions of years.<sup>[12]</sup> During this time period, pathogens have changed virulence to get used to the host's immune system. This is contradictory to the speciation of antimicrobial resistance that is a relatively recent event mostly in the last five decades following antibiotic discovery. Thus tolerance and virulence are thought to have developed during different eras. Both processes share common features irrespective of genetic variations, and both mechanisms are essential for the survival of microbes under unfavorable conditions. Antibiotic resistance allows bacteria to overcome therapies, and it is necessary to combat the host immune system by virulence. Second, horizontal genetic recombination is the process used to transmit factors around genera or species by both resistance and pathogenicity. <sup>[13]</sup> Although some mechanisms such as adaptive or punitive mutations may play their part, the transition of MGEs may be the key genetic process for resistance and pathogenic mutations allocation and co-selection. Thirdly, antibiotic resistance is also linked with virulence in the case of intracellular or biofilm producing bacteria. Consequently, cell wall alterations, porins the major contribution of efflux pumps, and two-component structures that stimulate or inhibit the expression of genes engaged in transmissibility and resistance are common characteristics for resistance and virulence.<sup>[14]</sup>



Figure 2: Mechanism of antibiotic resistance and virulence

Various antibiotic resistance processes along with drug efflux with the help of an efflux pump, enzymatic antibiotic alterations, enzymatic antibiotic breakdown, and target site alteration.

# Stopping spread of antibiotic resistance saves lives [20]

Acknowledging this menace requires constant aggressive action.

- Preventing infections from the first place.
- Slow resistance development through improved antibiotic use.
- Stop resistance spreading when it develops.

Without action, these germs can spread like wildfire - infecting and killing thousands of people each year.

Antibiotic-resistant pathogens can transmit among people with and without infectious symptoms. Depending on the germ, germs can transmit to people in many ways: for example, close contact (directly or indirectly) with a person who carries a resistant germ may occur when health care providers move from one patient to another by washing their hands.

In the air, for instance, TB bacteria may enter the air when a person with TB pulmonary disease or throat coughs, speaks, or sings<sup>[25]</sup>

- Polluted water, including sewage systems, hospital plumbing, or recreational water
- Contact with polluted particles, such as hospital rooms, kitchen counters, shared equipment (e.g., ultra sound machines), or personal belong-ings (e.g. towels)
- Animals- Eating tainted food or handling animals carrying resistant germs, for example
- sexual intercourse with a person bearing a resistant germ (e.g., N. gonorrhoeae or Shigella)

#### Therapeutic stratagies to combat antibiotic resistance

Infection control has long been a major concern of the genetic community, irrespective of the clinical evidence that small molecule monotherapy-based methods are ineffective in resistance environments. Evaluation of different candidates for infection control under process of development indicates that work should concentrate on antibiotic exploration and recognition of novels. Sadly, bio-therapeutics such as antibiotics, novel topical therapies and drug delivery methods are still lagging behind the development of new molecules that are typically an expansion of the current drug category. Systemic combination therapy methods where the drug discovery has been overtaken by resistance are ineffective worldwide. Instead of battling bacterial development, thus, control strategies could be better served by following resistance processes based on biological inspiration, such as furanones employed by red sea algae to disrupt the quorum sensitivity of resistant bacteria. <sup>[29]</sup>

Although the role of biologics in controlling bacterial infection is in its infancy, we can not overlook its potential to fight MDR. Small molecules would always have a key role to play in managing the infection; however, the quest for an effective drug candidate may be undertaken more logistically on the basis of biological inspiration. Various tools used for drug development are essential to address biological deficiencies, such as controlled delivery options, partial in vitro stability, inadequate high-throughput, advanced screening tools, inefficient pharmacokinetics, and relatively unknown pharmacodynamics, and are not as radical as those available for small molecular development. There is by chance a vast potential between combinations of biologics, biologically influenced molecules and methods for drug delivery. A paradigm shift including cancer and emerging viruses could therefore be modified to kill susceptible bacteria, control antibiotic resistance and protect the host microbiota. By combining conventional antibiotics, novel adjuvants, and viable limited delivery strategies, this type of approach can be crafted. Unlike various costly development models that often fail in trials, advanced bioinformatics will possibly bring substantial benefits to determine effective combination delivery and new targets. <sup>[26]</sup>

Application of different antibiotic resistance methods is quite important, as this has a significant impact on human beings and livestock. Given the excitement of the resolutions, with few being flung to solve the issue, to date little or no action has been taken towards these remedies. At present, antibiotics are compulsory in health settings, and due to unorganized efforts, the economic, social and medical fees would be cataclysmic. In the face of rising antibiotic resistance, the effect of antibiotics appears increasingly bleak. In developing therapy strategies to control infections, observational studies trends in MDR bacteria need to be considered. [28] Optimistically, constant highlighting of the problem would encourage researchers to adopt new strategies to control bacterial infection with the following criteria: discovery of new antibiotics, anticipation and prevention of antibiotic resistance, and host microbiota protection. For example, guided nanoparticles, liposomes, and infectionresponsive polymer-controlled delivery would help form novel combination strategies along with smart and local delivery tools.

Use of nanotechnology is emerging in medicine and it is not surprising to see the use of such techniques to handle the danger of antibiotic resistance. These may be paired with existing antimicrobials to improve their physiochemical activity against drug-resistant microbes. While the main antibiotic targets include inhibition or disruption of both the bacterial cell wall, protein inhibition, and nucleic synthesis, nanoparticles are reported to affect the respiration system and thus generate oxidative stress which lead to bacterial death. Nanoparticles also aim the bacterial cell wall, so silver nanoparticles could be combined with the appropriate antibiotics to improve their antimicrobial action through synergy, for example.

Antimicrobial peptides (AMPs) are new antimicrobial factors found in animals, microorganisms, and plants and to have an incredibly active broader spectrum against various bacteria, fungi, and protozoa. The amphipathic nature of AMPs allows for interaction and insertion of microbes into the cell wall and cell membranes. Although AMPs usually show antimicrobial activity due to damage to the cellular membranes,

Antibiotic class	Example(s)	Mode(s) of resistance
P-Lactams	Penicillins, Cephalosporins, Penems, Monobactams	Hydrolysis, efflux, altered target
Aminoglyco- sides	Gentamicin, Streptomycin, Spectino- mycin	Phosphorylation, acetylation, nucleotidyla- tion, efflux, altered target
Glycopeptides	Vancomycin, Teicoplanin	Reprogramming peptidoglycan biosynthesis
Tetracyclines	Minocycline, Tigecycline	Monooxygenation, efflux, altered target
Macrolides	Erythromycin, azithromycin	Hydrolysis, glycosylation, phosphorylation, ef- flux, altered target
Lincosamides	Clindamycin	Nucleotidylation, efflux, altered target
Strepto- gramins	Synercid	Carbon-Oxygen lyase, acetylation, efflux, al- tered target
Oxazoli- dinones	Linezolid	Efflux, altered target
Phenicols	Chloramphenicol	Acetylation, efflux, altered target
Quinolones	Ciprofloxacin	Acetylation, efflux, altered target
Pyrimidines	Trimethoprim	Efflux, altered target
Sulfonamides	Sulfamethoxazole	Efflux, altered target
Rifamycins	Rifampin	ADP-ribosylation, efflux, altered target
Lipopeptides	Daptomycin	Altered target
Cationic pep- tides	Colistin	Altered target, efflux

Table 1: Representing the mechanism of drug resistance of common antibiotics <sup>[19]</sup>

they can target other proteins, DNA, RNA, and regulatory enzymes and thus appear to be a promising substitute for classical antibiotics. However, development of resistance to AMPs is expected as soon as AMPs are used in clinical practice; therefore, exploring molecular mechanisms of their action is essential and a better understanding of the resistance against these compounds is necessary for rational planning in the use of AMPs as just an alternative to antibiotics. [30]

#### Domestic gaps to fight antibiotic resistance <sup>[25]</sup>

Improved implementation of infection prevention and control systems and antibiotic stewardship across the national and local health continuum tools and technology for identifying and reacting to antibiotic-resistant threats in health care, food, the environment and the community

- Greater implementation of infection prevention and control programs and antibiotic management across the single health spectrum
- State and local access to health care, food, environment and community tools and technology to detect and respond to antibiotic-resistant threats
- National data on antibiotic use across settings
- Local data on antibiotic resistance to help departments in public health identify where antibiotic resistance is increasing and inform the response to the outbreak
- Expanded health care workforce to help identify where antibiotic resistance occurs locally and introduce effective local response

• Increased collaboration between public health and health services to prevent germ spread and improve the use of antibiotics.

#### Innovation gaps to fight antibiotic resistance <sup>[25]</sup>

The global community needs new solutions, including the United States, which can enhance current practices and protect people and animals:

- Type in anything that you want. Then click Quill It on the right to paraphrase your input.
- Reliable diagnostics, including at the point of care, to support early detection and improved use of antibiotics and improve decision-making by health care providers and veterinarians.
- Better understanding of the microbiome, and how infection can be prevented and treated
- Better strategies to prevent spread in healthcare and in the community
- Effective antibiotic stewardship approaches, wherever antibiotics are used
- Better understanding of environmental antibiotic resistance and its effects on human and animal health
- Predictive analytics to help identify actions necessary to prevent resistance from spreading through human and animal health facilities, food, the community and the environment

#### Global action plan to control the menace of antibiotic resistance [24]

AMR's global burden has no signs of receding, but rather the pressure on human and veterinary medicine is piled up. Scientists and clinicians were not up to the minute about AMR until the first decade of the current century, whereas resistant bacteria had been identified before penicillin was discovered. Developmental phases are on the horizon for such global health concerns; for example, a book called "The emerging challenge of antimicrobial resistance – options for action" is a valuable addition to the collection.

Several countries around the globe have reported control of multiple resistant pathogens, especially MRSA, but the justifications behind the decline in these microorganisms ' resistance are disputed. For instance, the obvious success of confining MRSA achieved in the US by following various hygiene and screening schemes has been cast aside because some additional factors, such as overall national decline in MRSA prevalence, may be a strong reason for MRSA regulation. The same acts have also been noticed dramatically at national level in Europe. Scientific fraternity needs to appreciate these claims, as we are still struggling to acknowledge the requirement for AMR regulation of major interventions. The eradication of AMR may not be achievable but it may decelerate its progression. Various global agencies such as the Global Antimicrobial Resistance Surveillance System under WHO should work to control antibiotic resistance; Food and Agriculture Organization, CDC and Office International des Epizooties are making strong efforts to control antibiotic resistance. Certain schemes addressing the growing threat of antibiotic resistance include the Global Health Security Agenda (GHSA), Action Package on Antimicrobial Resistance.

The misconception about AMR's enormity and risk has mapped the new epidemic. Additionally, studies that show AMR's burden influenced the think tanks to urge them to peruse the issue. Countries which have developed inclusive national plans continue to be successful in controlling AMR. These methods include careful antibiotic use, antibiotic monitoring using the "One Health Approach," advancing health care setup, developing health insurance policies, restricted drug promotion, coherent disease control strategies and community stewardship plans. Such techniques, on the other hand, take patience and time to plan. Furthermore, these require a thorough support with sufficient funds from the government authorities. Progress in developing countries is at a very low pace, although some Asian countries, including India, have recently taken some courageous steps towards AMR control; For example, a declaration from Chennai. Diagnostics have a significant impact on the establishment of AMR, as it impels clinicians to use antibiotics imprudently. Especially in developing countries, diagnostics is a pressing issue because they still rely on conventional microbiological tools to identify bacteria. The advancement of personalized medicine based on new and effective molecular diagnostic tools that would be very helpful in identifying patients who really need antibiotic therapy could fill those gaps. One Health Approach could be a very useful tool to study

the interaction between humans and animals, and to direct researchers to design new screening instruments. This topic is of particular significance and must be taken seriously because the AMR transmission pathway has been formed between all components (human, animal, and environment) of one health. Antibiotic unwise and irrational use is also a prominent factor associated with AMR, especially in low-and middle-income countries (LMIC). For many reasons, antibiotics are used imprudently, such as patient satisfaction with a physician's prescription, inappropriate information on antibiotics, inappropriate diagnosis, quackery, especially in developing countries, and, sincerely, pharmaceutical industry temptations for doctors. Having a dearth of new antibiotics, dealing with this portion of the problem is quite difficult. Antibiotic innovation, combination therapy, and technological development are essential.<sup>[21]</sup> The integration of the health care system and antibiotic stewardships is another aspect of colossal importance here. Data on the health and economic impact of AMR on developing countries are inadequate. LMICs are in a dire situation as regards the clinical outcomes of many fatal bacterial diseases such as neonatal sepsis, typhoid, etc. Therefore, the job is not just to use traditional options but also to implement some personalized control policies; Resistant pathogens should, for example, be given priority as MDRM. Tuberculosis: Tuberculosis WHO recommendations regarding infection and disease control should be followed up to tertiary level. Comprehensive data should be gathered by taking into consideration all national stakeholders including government, academia, and industry. In fact, the interaction between industry and academia should be strengthened because both academia and industry have made some profound mistakes in the past. First, in the late 20th century, academics and researchers had a mistaken belief in the elimination of infectious diseases and huge amounts of antibiotics created by industry. Second, though financial incentives in the form of research grants have been given to the academic and pharmaceutical industries, an insufficient proportion has been allocated to academia and industries to generate sufficient new classes of antimicrobial agents compared with the increase in antibiotic resistance. In expiation, a group of experts known as the American Infectious Disease Society proposed a proposal of 10 to 20; this was about the creation of 10 new safe and effective antibiotics by the end of 2020.

The use of alternative therapies for treating and managing infectious diseases could also be another and a popular method to fend off AMR. Other therapies include techniques for anti-virulence (to interact with the bacterial virulence factors), biological therapies (use of monoclonal antibodies, insulin, erythropoietin, etc.), as well as vaccines (MRSA vaccines, MDR tuberculosis vaccines). In addition, herbal medicines have elusive properties; there is a strong point of view that they could be a viable alternative option.

# CDC (centers for disease control and prevention) assessment of antibacterial resistance threats [30]

# **Urgent Threats**

- Clostridium difficile
- Carbapenem-resistant, Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae

# **Serious Threats**

- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococci (VRE)
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant nontyphoidal Salmonella
- Drug-resistant Salmonella Typhimurium
- Drug-resistant Shigella
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Drug-resistant Streptococcus pneumoniae
- Drug-resistant tuberculosis

# **Concerning Threats**

- Vancomycin-resistant Staphylococcus aureus (VRSA)
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

# CONCLUSION

In developing and developed countries there are distinct socio-economic and political factors leading to antibiotic resistance. The primary contributors to the development of resistance in developing countries include poor monitoring of drug-resistant infections, poor quality of available antibiotics, clinical misuse and the ease of antibiotic availability. While factors such as self-medication and lack of regulation on medication imports play a role in developed countries, key factors in developed countries, by contrast, include poor regulation of hospital-based antibiotic use and excessive use of antibiotics in animals that produce food. Finally, work on novel medicines is declining to continue fighting infections.

To tackle antibiotic resistance, two key elements are essential: (1) strengthening the regulatory framework for global control of antibiotic use, and (2) fostering research on novel antibiotics. To maintain consistency across nations, it is important to have clear guidelines that are set in place by an International Health Agency, such as the WHO. However, since each country has a different health care and regulatory system, it would be necessary to leave specific policies for managing antibiotic use to the individual nations. The regulatory system needs to be further improved on the basis of the specific challenges that must be addressed in that country. The manufacturing process, quality, availability and use of antibiotics in developing countries needs to be further controlled, hospital-based interventions and antibiotic use in food-producing animals in developed nations need to be regulated.

The WHO is currently taking steps in the right direction, as it has developed a Global Antimicrobial Resistance Surveillance System (GLASS) that partners with regional and national antimicrobial resistance surveillance systems to provide accurate and timely data.

Similar efforts to regulate each of the contributing factors would help lower the rate of development of the resistance globally.

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